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炎症在衰老与衰老相关疾病中的作用及机制研究进展

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【摘要】中国人口老龄化问题日趋严峻。延缓组织器官衰老，预防和治疗衰老相关的疾病，制定干预和延缓衰老的安全有效策略已成为亟待解决的重要科学问题。慢性炎症累积促进细胞及机体衰老，是多组织器官衰老的共性特征之一。本文综述了炎症在衰老及衰老相关疾病中的作用及调控机制，以及靶向干预炎症信号延缓衰老的最新研究进展。

【关键词】衰老；炎症；衰老相关疾病；炎症信号靶向干预

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New research progress on the role and mechanism of inflammation in aging and aging-related diseases

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【Abstract】The problem of aging population in China is becoming increasingly severe. Intervening aging and its related diseases, developing safe and effective strategies to delay aging process have become urgent scientific issues. Accumulation of chronic inflammation, a common feature of multi-tissues in the elder, promotes cell and organism aging. This article reviews the role and underlying mechanisms of inflammation in aging and age-related diseases, as well as the anti-aging interventions targeting on inflammatory signals.

【Keywords】Aging; Inflammation; Aging-related diseases; Targeted intervention of inflammatory signals

据统计，2021年全球65岁及以上人口为7.61亿，到2050年这一数字将增加到16亿[1, 2]。当60岁以上老龄人口比例接近10%时，提示社会人口趋向老龄化。截止2021年末，中国老龄化人口比例已达18.9%，即将进入中度老龄化社会[3]。人口老龄化的加剧和衰老相关疾病的高发已成为中国乃至世界面临的重大社会问题。衰老是一种复杂的生物学过程，导致组织器官稳态、机体功能、应激能力和再生能力的显著下降[4]。此外，衰老是神经退行性疾病、心脑血管疾病、骨关节炎和慢性肾脏疾病等众多慢性疾病的主要风险因素[5-8]。因此，针对衰老的研究正在进入一个对医学和社会具有独特意

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义的新阶段。如何延缓衰老及衰老相关疾病的发生发展，已成为当今老龄化社会亟需解决的重要科学问题。

解析衰老的分子特征以及调控机制，是发展延缓衰老的干预手段、防治衰老相关疾病的理论基础。慢性炎症累积驱动细胞及机体衰老，是众多组织器官衰老的共性特征[9]。越来越多的研究表明[10]，慢性炎症是许多衰老相关疾病的主要危险因素，广泛而深刻地参与众多衰老相关慢性疾病，例如心血管疾病、神经系统疾病、代谢疾病以及免疫系统疾病的发生发展。此外，高水平的炎症信号累积，导致老年人对炎症反应更加敏感，增加了老年人对感染的脆弱性，进一步加剧了感染导致的众多并发症[11]。阐明慢性炎症的信号传导和作用途径，明确炎症调控衰老的分子机制，挖掘可干预的炎症信号靶点，对延缓衰老以及干预、治疗衰老相关疾病具有巨大潜力。本文综述了炎症在衰老及衰老相关疾病中的作用及调控机制，以及靶向干预炎症信号缓解衰老的最新研究进展。

1 炎症累积促进细胞及机体衰老

慢性炎症累积是衰老的重要特征，参与衰老过程并与衰老相关疾病的发生发展密切相关[12]。伴随着衰老，肠道生态失调，代谢异常，激素水平改变，衰老细胞累积以及免疫系统衰老等众多因素促进了慢性炎症的累积[13]。与急性炎症不同，慢性炎症的特征是即使在没有急性感染和临床诊断性疾病的情况下，保持低度、持续的炎症背景[14, 15]。这种与年龄相关的无菌、持续的炎症通常被称为“炎症性衰老”（Inflamm-Aging）。转录组测序显示，衰老组织中炎症相关基因及信号通路显著上调[16-18]。同时，老年人血液中的C-反应蛋白（C-Reaction Protein，CRP）、白细胞介素-6（Interleukin-6，IL-6）和肿瘤坏死因子（Tumor Necrosis Factor-α，TNF-α）等促炎因子水平升高[19, 20]。衰老过程中衰老细胞增多，伴随细胞衰老出现衰老相关分泌表型（Senescence-Associated Secretory Phenotype, SASP），进一步加剧了机体的炎症反应[15]。此外，慢性炎症不但伴随着衰老累积，反过来还会促进细胞及机体衰老[14, 21, 22]。衰老时高水平的促炎因子TNF-α、IFN-γ和IL-6等通过自分泌及旁分泌途径加速机体的衰老进程[23, 24]。炎性细胞因子TNF-α通过PI3K/Akt信号通路促进大鼠髓核（Nucleus Pulposus, NP）早衰[25]。年轻细胞外源添加IL-6或可溶性IL-6Rα培养后，出现生长停滞和衰老相关-β-半乳糖苷酶（Senescence-Associated-β-galactosidase, SA-β-gal）活性上升等衰老表型[26]。因此，靶向干预炎症信号为延缓衰老及衰老相关表型提供了新思路。

成体干细胞对于维持机体和器官的稳态至关重要。在衰老过程中，慢性炎症的累积会导致干细胞的衰老，进而影响多种组织器官的长期稳态维持。聚肌胞苷酸（Polyinosinic-polycytidylic acid, Poly I:C）作为Toll样受体3（Toll-Like Receptor 3, TLR3）激动剂常用于模拟无菌性炎症，连续的poly I:C刺激导致年轻小鼠的造血干细胞加速衰老，促使年轻小鼠出现衰老相关的贫血表型[27]。与年轻的造血干细胞相比，衰老造血干细胞表达更高水平的NF-κB，导致其在炎症刺激后的消退阶段无法下调炎症信号进而加剧炎症的累积。炎症的累积与衰老造血干细胞在应对炎症刺激后更快的丧失自我更新能力并偏向髓系分化密切相关[28]。以上的研究提示，衰老会进一步加剧炎症反应的不良后果。衰老时慢性炎症的累积与老年人感染风险增加、疫苗接种反应差密切相关[29]。老年人具有较高的循环细胞因子、趋化因子和急性期蛋白水平[14, 30]。IL-6的持续升高会引发肺组织的炎症和损伤并促进病毒的复制[31]。老年人血清中富集的TNF-α和IFN-γ等炎症因子过度激活JAK/STAT1信号通路，进而上调细胞表面SARS-CoV-2受体表达，导致老年人对COVID-19的易感性增加[32-34]。处于系统性慢性炎症状态的老年人在感染时更容易产生细胞因子风暴等更严重的炎症反应，这可能会减弱机体的抗病毒反应，进而导致老年人在受到感染后出现更严重的不良反应[31]。此外，在慢性感染的情况下，炎症信号刺激导致$CD8^+$ T细胞功能下降，T细胞受体（T Cell Receptor, TCR）多样性显著降低，T细胞的效应器功能逐渐丧失等T细胞功能耗竭表型[35, 36]，最终表现为老年人对灭活疫苗的反应延迟[37, 38]。综上所述，炎症累积加速细胞及机体衰老，衰老会进一步加剧炎症的累积，导致老年个体在面对感染时出现更严重的不良反应。

2 炎症累积促进衰老相关疾病的发生发展

慢性炎症累积促进众多组织器官衰老相关疾病的发生发展[39, 40]，炎症累积诱发并促进克隆造血、髓系白血病、贫血、心力衰竭和动脉粥样硬化等造血和心血管系统相关疾病。此外，炎症相关的造血、心血管疾病的发生进一步通过血液循环系统导

致衰老个体的多组织器官炎症水平升高和功能紊乱。我们以造血和心血管系统为例，综述炎症对衰老相关疾病的作用。

伴随着衰老，骨髓造血干细胞中出现DNA突变的累积，部分突变赋予造血干细胞克隆性扩增优势，导致携带突变的造血干细胞克隆伴随着衰老逐渐增多，并且对成熟血液细胞的产生起主导作用，被称之为意义未明的克隆造血（Clonal Hematopoiesis of Indeterminate Potential, CHIP）[41-44]。在70岁以上的人群中，高达20%的人携带CHIP，因此，CHIP也称为“与年龄相关的克隆性造血”（Age-Related Clonal Hematopoiesis, ARCH）。克隆造血已成为人类衰老新的重要生物标志物之一，其潜在的临床意义正逐渐被认知。ARCH不但促进了血液系统疾病的发生，更重要的是，ARCH携带者患心肌梗死、中风和动脉粥样硬化等心血管疾病风险增加，并且与全因死亡率增加密切相关[45-47]。

突变累积是克隆造血的内在驱动力，最新的研究发现[48]，炎症是诱发及推动克隆造血的重要因素。炎症促进造血干细胞分化，而过度的分化诱导造血干细胞自我更新能力耗竭[49]。然而，携带*Dnmt3a*、*Tet2*等主要驱动克隆造血突变的造血干细胞耐受炎症诱导的分化，进而在慢性炎症累积的过程中促使携带突变的造血干细胞获得扩增优势，诱发克隆造血[50, 51]。反过来，克隆造血促使造血髓系分化偏斜，导致ARCH患者外周血中出现更高水平的IL-6、TNF-α、IL-1β和IL-18等促炎因子[52, 53]。此外，最新的研究发现[54]，动脉粥样硬化疾病的发生发展反过来可以进一步推动克隆造血。因此，慢性炎症累积、动脉粥样硬化等衰老相关疾病和克隆性造血之间出现恶性循环，进一步通过血液循环系统促进衰老个体的多组织器官炎症水平升高和功能紊乱。随着新技术的发展，目前通过细胞游离DNA（cell-free DNA, cfDNA）测序技术检测CH的发生已具有可行性[55]。鉴于炎症对于克隆造血的重要推动作用，明确炎症推动克隆造血的机制，探索潜在的炎症干预靶点对缓解衰老及治疗衰老相关疾病具有重要的研究意义。

3 靶向干预炎症信号缓解衰老

慢性炎症累积、DNA损伤积累、端粒缩短、抗细胞凋亡信号激活、表观遗传修饰变化、细胞周期抑制蛋白表达增加等众多因素促进衰老[12]。以往的研究表明[56, 57]，靶向干预炎症信号是延缓衰老的重要途径。例如，在老年小鼠的皮肤中特异性抑制炎症信号中的关键转录因子NF-κB，能够促进老年小鼠的皮肤组织年轻化，并且使其在转录水平上类似于年轻小鼠[58]。异体共生模型研究发现，老年小鼠血液中的促炎因子诱导年轻小鼠的细胞和组织衰老，导致肝纤维化、近端肾小管损伤、肌肉力量下降等多组织器官的衰老表型的出现[59, 60]。相反，年轻小鼠血液含有的凝集素能够通过抑制炎症信号改善老年小鼠大脑的认知功能[61]。鉴于炎症信号途径分子机制明确，且易于靶向干预[62]，因此，靶向炎症因子对临床上干预及治疗衰老相关的疾病具有重要的意义和应用价值。通过干预生活方式，包括节律调节、饮食限制以及运动等手段，可以有效抑制炎症，干预衰老及衰老相关疾病。

3.1 靶向清除衰老细胞缓解衰老

在衰老过程中，生物体在器官、组织、细胞及分子水平上均发生一系列的改变，其中衰老细胞的累积对个体衰老进程起关键作用[63, 64]。Baker等[65, 66]研究发现，在早衰小鼠模型以及自然衰老小鼠中选择性清除*P16*阳性衰老细胞可以延缓衰老小鼠机能下降，并延长其寿命。此外，Kirkland团队[67]证明移植少量的衰老细胞到年轻小鼠体内足以引起持续的机体功能障碍，诱发年轻小鼠衰老。表明细胞衰老能够促进个体衰老，而清除衰老细胞可以有效地缓解衰老。

与年轻细胞相比，衰老细胞具有更强的抗凋亡能力。针对这一特性，Kirkland团队[68]通过筛选抗细胞凋亡阻断药物，发现达沙替尼和槲皮素组合，即一代选择性清除衰老细胞的药物senolytics可以有效清除衰老细胞。通过清除衰老细胞可以减少脂肪组织中IL-6、IL-8及GM-CSF等促炎细胞因子的分泌，进一步抑制衰老细胞诱导的SASP[68]。此外，通过靶向衰老细胞特异性表达的β-gal，衰老特异性杀伤化合物SSK1可以有效地清除多种组织中的衰老细胞，减轻局部和全身炎症并恢复衰老个体机能[69]。由于大部分清除衰老细胞的药物具有较大的毒副作用[70]，越来越多的研究将目光转向天然产物的开发和应用。研究人员发现，高浓度的葡萄籽提取物中类黄酮原花青素C1（Procyanidin C1, PCC1）可以通过诱导细胞凋亡以及线粒体功能障碍杀死衰老细胞，提升机体功能延缓衰老[70]。由于天然产物具有易吸收，低毒性等优势，从天然产物中筛选senolytics药物具有巨大的应用前景。

虽然衰老细胞累积促进机体衰老，但越来越多

的研究发现衰老细胞在伤口愈合、抑制癌症以及维持组织器官结构稳定等方面起到重要作用。因此，清除衰老细胞对于整个机体的健康状态具有潜在的风险。研究显示[71]，*P16*阳性的衰老成纤维细胞通过促进IL-6的分泌进而诱导上皮组织再生，清除肝脏中衰老的内皮细胞会导致组织的纤维化，影响组织的结构和功能[72]。通过分泌血小板衍生生长因子AA（Platelet Derived Growth Factor AA，PDGF-AA），衰老细胞可以诱导肌成纤维细胞分化，加速伤口闭合[73]，提示衰老的成纤维细胞和内皮细胞在伤口愈合的过程中发挥重要作用。因此，亟需一种相对温和的延缓衰老的药物，在维持衰老细胞重要生理功能的前提下缓解衰老。

3.2 靶向抑制SASP因子缓解衰老

衰老细胞的一个重要特征是SASP，即衰老细胞分泌众多炎症因子、趋化因子、生长因子和蛋白酶等。不同于senolytic，senomorphics不诱导衰老细胞凋亡，而是通过靶向抑制SASP，进而达到延缓衰老的目的[74]。二甲双胍、芹菜素和山茶酚等类黄酮化合物[75-78]和NF-κB抑制剂BAY11-7082[79]可以通过干预关键炎症信号通路传导进而抑制SASP。靶向促炎因子IL-6、IL-1α、IL-1β和TNF-α的中和抗体，也显示出对衰老相关疾病的有效干预[80-82]。其中，IL-6作为一种重要促炎因子，参与众多衰老相关疾病的发生发展。靶向IL-6及其受体的单抗，例如tocilizumab、sarilumab和siltuximab已广泛应用于临床治疗骨关节炎和COVID-19等衰老和炎症相关疾病[83]，但靶向促炎因子的单抗往往由于价格高昂而限制其广泛的应用。天然产物具有价格低廉，低毒副作用及不含合成化学物质等特点，越来越多的天然药物来源的senomorphic药物逐渐被开发应用。姜烯酮A是生姜提取物中的成份之一，具有良好的抗炎抗衰老特性。姜烯酮A可以显著抑制衰老成纤维细胞分泌促炎因子IL-6、CCL2（MCP-1）和IFN-γ诱导蛋白10（IP-10），促进抗炎因子IL-10和IL-13的生成[84]；芹菜中富含芹菜素，芹菜素通过抑制IRAK1、IRAK4、p38-MAPK的磷酸化和NF-κB的活性，从而部分抑制SASP，减少衰老细胞对癌症等年龄相关疾病的影响[85, 86]；柚皮素是最重要的天然黄酮类化合物之一，主要存在于葡萄、橙子和柠檬等柑橘类水果中。柚皮素已被证明可通过抑制TNF-α信号通路来改善衰老小鼠大脑中的神经发生，也可有效抑制SASP，缓解衰老引起的肺部纤维化[87, 88]。

值得注意的是，基于senomorphics的延缓衰老策略仍具有潜在的风险和不确定性。众多SASP因子在调控免疫反应、抑制炎症、促进组织再生及抗肿瘤中有重要作用，因此靶向递送药物系统的开发对senomorphics药物的推广具有重要意义。此外，senomorphics药物需要连续、长期的使用才能维持抑制SASP的效果，长时程连续服用senomorohics的毒副作用有待更深入的研究。

3.3 通过节律调节，饮食限制和运动抑制炎症缓解衰老

最近的研究表明[9]，环境和生活方式的改变，包括昼夜节律、饮食、体育运动、工业毒物等促进系统性慢性炎症累积，进而导致多种衰老相关疾病的发生发展。调节生活方式将为抑制炎症和延缓衰老提供一种低成本和长期有效的替代策略[89]。

昼夜节律系统调控哺乳动物的行为和生理节律，参与调控包括神经、免疫系统稳态平衡、代谢及氧化应激反应等众多生理病理过程[90-92]。唤醒及睡眠时间等节律发生改变，导致高敏CRP升高。长期持续的昼夜节律失调促进慢性炎症累积，诱发心血管疾病[93, 94]。此外，研究发现昼夜节律改变加速炎症刺激后小鼠的死亡[95]，而调控昼夜节律的关键基因如*Clock*、*Bmal1*的缺失也会导致小鼠出现慢性炎症累积及衰老相关表型[96, 97]，因此，调控昼夜节律可以通过调控炎症累积进而影响衰老的进程。

除昼夜节律的调控外，热量限制（Caloric Restriction, CR）也是有效的干预衰老的措施之一[98]。最新的基于单细胞转录水平的研究发现[99]，CR通过下调NF-κB等关键炎症信号通路，显著抑制大鼠多组织器官的炎症因子表达。在棕色脂肪组织、白色脂肪组织、肝脏和肾脏组织中，CR明显抑制中性粒细胞堆积，减少肝组织和脂肪组织中巨噬细胞浸润[100]。此外，CR诱导衰老白色脂肪、皮肤和主动脉中巨噬细胞从促炎状态转变为抗炎状态[101]。通过抑制衰老机体炎症因子，CR可显著改善造血干细胞衰老表型，提示CR可以通过抑制炎症维持组织特异性干细胞功能，进而产生持续性延缓衰老的效果。值得注意的是，CR在减缓炎症的同时也会损害免疫系统。实验显示，长时间禁食会引起各组织中白细胞数目减少，促进骨髓中*CXCL4*基因的高表达以及单核细胞留存在骨髓。这些留存骨髓中的单核细胞，在进食后的4个小时内会重新回到血液中，但它们并不能抵抗感染，反而导致循环中单核细胞的激增，加剧了炎症，使得

机体抵抗感染的能力下降，导致更高的死亡率[102]。因此，CR是一把双刃剑，CR可以延缓衰老，但也对免疫细胞产生较为负面的影响。

周期性规律运动作为区别于热量限制的调控方式，可以抑制多组织器官中炎症累积[103]。多个基于大队列人群调查研究发现[104, 105]，运动可以显著降低60岁以上衰老人群血清中IL-6、TNF-α和CRP等炎症因子水平。与此同时，运动也可以通过降低活性氧水平以及增加细胞抗氧化能力，抑制活性氧累积诱导的炎症反应，进而延缓衰老[106]。一项最新的研究发现，运动通过降低瘦素的表达，使得造血干细胞/祖细胞维持于静息期，并减少了循环白细胞的数量，进而抑制炎症因子表达，最终降低急性心肌梗死及动脉粥样化等心血管疾病的患病风险[107]。衰老相关的克隆造血对血液系统和多组织器官衰老及衰老相关疾病的发生发展起重要的促进作用，运动是否可以缓解克隆造血从而调控衰老值得深入探究。

4 总结

慢性炎症是促进细胞及机体衰老，增加衰老相关疾病风险的重要因素。靶向干预炎症信号是缓解衰老及促进组织再生的有效手段，但该领域仍面临巨大的挑战。目前，不论是清除衰老细胞的senolytics药物还是抑制衰老细胞SASP的senomorphics药物，都具有潜在风险。衰老细胞具有维持组织结构完整性、促进损伤修复等作用；众多炎症因子在调控免疫反应，促进组织再生及抗肿瘤中具有积极作用。无差别的清除衰老细胞，以及整体性抑制炎症信号将导致部分组织结构紊乱及免疫功能异常。因此，开发组织器官靶向药物递送技术以及探明干预的最佳时机，将极大的降低应用药物诱导衰老细胞清除及抑制SASP途径抗衰老的潜在风险。此外，现有的药物多需长期服用且价格高昂，开发天然产物来源的促进衰老细胞清除及抑制SASP的药物具有巨大的应用前景。区别于应用药物干预衰老，调节生活方式是一种低成本、易持续且更安全的干预手段。然而，在减缓炎症延缓衰老的同时，CR也损害了机体的免疫系统。最近在果蝇模型的研究表明[108]，不用做到CR，维持果蝇的饥饿感就能够达到延缓衰老的目的。在将这些发现应用于人类之前应谨慎行事，但这项研究提示，完全有理由期待所发现的机制可能会调节其他物种的饥饿驱动进而延缓衰老。

总体来讲，虽然靶向干预炎症缓解衰老的策略还存在诸多限制，但是近年来人们在这个领域的探索已经取得了很大进展。在未来，应用新技术，在全新的角度解析炎症调控衰老的分子机制将为挖掘缓解衰老提供新靶点。建立合适的炎症衰老动物模型，明确衰老过程中炎症的来源，解析促炎与抑炎信号之间的转换机制，阐释多组织器官炎症衰老的共性调控机制，寻找炎症衰老的生物学标记物等多方面的进一步探索将有助于深入理解炎症与衰老的关系，为缓解人类衰老促进衰老组织器官再生提供重要的理论基础。

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